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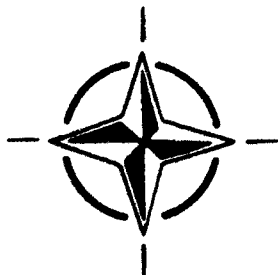
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## **Nutrition, Metabolic Disorders and Lifestyle of Aircrew**

(Les Désordres Métaboliques Dus à la Diététique  
et Hygiène de Vie des Equipages d'Aéronefs)

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# Effects of Caffeine on Mental Performance and Mood: Implications for Aircrew Members

Harris R. Lieberman, Bernard J. Fine, John L. Kobrick  
and John D.E. Gabrieli<sup>1</sup>

Military Performance and Neuroscience Division  
Occupational Health and Performance Directorate  
U. S. Army Research Institute of Environmental Medicine  
Natick, MA. 01760, U.S.A.

Department of Psychology<sup>1</sup>,  
Stanford University, Stanford, CA 94305, U.S.A.

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## 1. SUMMARY

Caffeine is generally regarded as the most widely used drug in the world. However, it is also a food constituent. Its acute effects on behavior appear to be greater than those of any other food constituent as they are detectable when caffeine is administered in doses found in single servings of coffee, tea and soft drinks. Caffeine affects the central nervous system by binding to adenosine receptors, and it has acute and chronic, dose dependent, effects on brain function. Low and moderate doses have beneficial effects on mental performance but high doses may have adverse effects. Tolerance develops to continued use of caffeine, so that its acute effects are altered when it is used chronically in high doses. Physical and mental symptoms associated with sudden withdrawal of caffeine have also been reported. The acute effects of caffeine on vigilance, simple and complex cognitive performance, and mood state are discussed. Doses equal to single servings of beverages consistently improve auditory and visual vigilance. In addition, moderate doses of caffeine increase self-reported alertness. The duration and magnitude of these effects on individuals are related to habitual caffeine consumption and interact with tobacco use. In view of its dose-related beneficial and deleterious effects, aircrew personnel, flight surgeons, military commanders and planners should have knowledge of the potential influence of caffeine on performance, especially vigilance, and mood, as well as the consequences of its abrupt withdrawal.

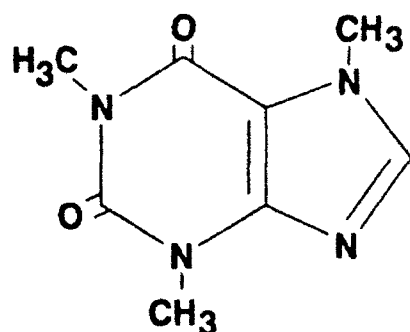
## 2. INTRODUCTION

A variety of food constituents have been studied to determine their potential influence on behavior. Tryptophan, tyrosine, phenylalanine, choline, caffeine, protein and carbohydrate have been administered to both humans and laboratory animals and their effects on a variety of behaviors evaluated (for a recent review see Lieberman, (1)). With the exception of caffeine, the literature on each substance is quite limited. Even so, it is apparent that when the magnitude of the behavioral effects

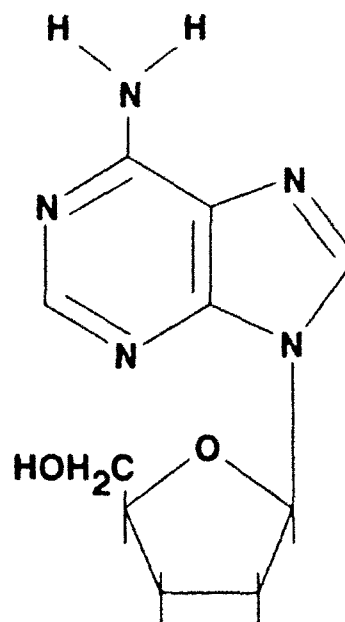
of food constituents are compared, caffeine is the most potent. When the effects of caffeine are contrasted to those of other food constituents on an equal weight-to-weight basis (i.e., 100 mg of caffeine versus 100 mg of any other food constituent) the magnitude of caffeine's effects appear greater. Furthermore, caffeine appears to have an even greater advantage when the comparison is based on the effects produced by single servings of common foods (1). The choline, tryptophan or carbohydrate, etc. that is found in a single serving of any food will not have effects that are as large or consistent as the those produced by the caffeine in a typical beverage (1). In fact, based on the currently available literature it appears that caffeine is the only food constituent that has been shown to unequivocally affect behavior when it is administered in the doses found in common foods (2). Of course, future studies may demonstrate that other foods have unexpected or greater effects on behavior.

## 3. CAFFEINE IN THE DIET

Caffeine (1,3,7-trimethylxanthine), theobromine (3,7-dimethylxanthine) and theophylline (1,3-dimethylxanthine) are naturally-occurring substances found in foods and drugs (Fig. 1). Of the three, caffeine is the most important since it is consumed in much larger quantities than the other two (2,3). In addition to being the xanthine found in coffee, caffeine, not theophylline, is the primary xanthine found in tea. In spite of reports in the popular press to the contrary, caffeine is much more abundant in tea than any other xanthine. By weight, tea leaves are reported to contain about 3.2 percent caffeine but only 0.03 percent theophylline. Trace amounts of theophylline are also found in coffee and cocoa. Theobromine is found in significant quantities in cocoa but it is not believed to be behaviorally active in the doses found in foods (4,5). Cola beverages also contain significant amounts of caffeine but most is added, although kola nuts, which are used to flavor colas, contain some naturally-occurring caffeine (2,5).



Caffeine



Adenosine

Figure 1. The structural formulae of the three methylxanthines found in foods and drugs (2).

Although there are considerable differences among the NATO countries in patterns of beverage consumption, there is good evidence that total caffeine intake is similar across nations. Coffee consumption is highest in the Scandinavian countries, followed by Germany, Canada and the U.S. and lowest in the United Kingdom and the Mediterranean countries (6). However, higher consumption of tea in the United Kingdom may substitute for lower consumption of coffee. In Canada about 60% of caffeine intake is from coffee and 30% from tea (6). Coffee is also the predominant source of dietary caffeine intake in the United States, with about 70% derived from this source and 15% from tea (5-7). It has been estimated that in Western Europe total daily caffeine intake is about 245 mg/day (6). Total per capita caffeine intake in the United States is approximately 195 mg/day (2,5,7,8).

In order to evaluate the effects that caffeine consumption may have on aircrew members it is essential to have accurate information on intake and temporal patterns of caffeine consumption. Unfortunately, gathering such information is a more difficult undertaking than might be supposed. Although there is considerable variation in the macronutrient composition of specific foods, it is generally possible, based on dietary records, to estimate the proportion of protein, carbohydrate and fat and arrive at reasonably reliable intake estimates. However, because caffeine and related compounds occur naturally in coffee,

tea and chocolate, there is considerable variability in their concentration before preparation. Furthermore, the method of preparation greatly increases variability in the caffeine content of the actual food or beverage. A weakly brewed beverage will contain considerably less caffeine than a strong one. Preparation is especially critical for coffee. Coffee prepared using the drip method contains, on average, the most caffeine, about 110 mg/cup, while instant (soluble) contains considerably less, about 60 mg/cup on average (Table 1) (2,5,9). In addition, each type of coffee can vary tremendously with respect to actual caffeine content. Roasted and ground coffee may contain from 40-150 mg/cup, while instant coffee has from 40-108 mg/cup (3,8,10,11). Arabica varieties of coffee, usually classified as higher quality on the basis of taste, contain substantially less caffeine than the lower quality robusta beans (2). Tea, most cola beverages and other soft drinks, typically contain less caffeine per serving than coffee. One cup of tea, as it is brewed in the United States, contains about 40 mg of caffeine and most colas 30-40 mg per 12 oz. serving (Table 1) (2).

Caffeine also is found in certain over-the-counter (OTC) and prescription medications. For example, the recommended dose of one North American OTC pain medication contains 64 mg of caffeine in addition to aspirin. A variety of OTC preparations, in which caffeine is the only active ingredient, are available in the United

TABLE 1

## CAFFEINE CONTENT OF SELECTED BEVERAGES AND FOODS\*

<u>Item</u>	<u>Caffeine Content (mg)</u>
Coffee (5-oz cup)	
Drip method	90-150
Percolated	64-124
Instant	40-108
Decaffeinated	2-5
Instant decaffeinated	2
Tea, loose or bags (5-oz cup)	
1-min brew	9-33
3-min brew	20-46
5-min brew	20-50
Tea products	
Instant (5-oz cup)	12-28
Iced tea (12-oz can)	22-36
Chocolate products	
Hot cocoa (6 oz)	2-8
Dry cocoa (1 oz)	6
Milk chocolate (1 oz)	1-15
Baking chocolate (1 oz)	35
Sweet dark chocolate (1 oz)	5-35
Chocolate milk (8 oz)	2-7
Chocolate-flavored syrup (2 tbsp)	4
Cola Beverages (12-oz)	
Coca-Cola Classic	46
Pepsi	38
Coke	46
RC Cola	36
Diet Pepsi	36
Diet Coke	46
Diet RC Cola	48
TAB	46
Other Soft Drinks	
Dr. Pepper	41
Diet Dr. Pepper	41
Mountain Dew	54
Mellow Yellow	52
Diet Mellow Yellow	12
Mr. Pibb	40

\* Lieberman (2).

States for use as stimulants. A dose of 100-200 mg is recommended by the manufacturers. Theophylline, often in high doses, is used to treat asthma. However, drugs probably account for only a small part of the total xanthine intake in the United States because so much of these compounds are consumed in foods. Flight surgeons, other medical personnel and individuals themselves need to be aware of these sources of caffeine, since the effects of such drugs will be additive with respect to dietary caffeine intake and, if consumed on a regular basis, they will produce tolerance to the effects of caffeine. Given the unusually large variation in caffeine content in common

foods, particularly coffee and tea, it is probably quite difficult to arrive at accurate quantitative caffeine intake estimates for individuals by using dietary records alone. However, it is not difficult to accurately classify individuals as low, moderate or high users of caffeine based on careful recording of daily consumption of caffeine-containing foods. When such estimates are compared to the individuals' plasma caffeine concentration there is reasonable agreement between the subjective and objective methods (Lieberman, unpublished observations). When estimates of caffeine intake for aircrew members are based on dietary surveys, it is important to consider duty

versus off-duty periods since caffeine consumption varies with the work-rest cycle (12). There appear to be little data in the literature concerning the use of caffeine by aircrew members. However Graeber (12), has documented high levels of caffeine use by commercial pilots when they are fatigued.

#### 4. CAFFEINE'S MECHANISM OF ACTION

Caffeine, when it is administered in the levels found in the diet, appears to act by blocking the effects of adenosine (13). Adenosine is a neuromodulator that is found throughout the brain and periphery. Several classes of receptors with selective affinity for it have been identified, including the  $A_1$  and  $A_2$  subtypes (14). Adenosine has been found to have potent inhibitory actions and the methylxanthines appear to act by inhibiting the binding of endogenously released adenosine at its receptor sites (2,5). Central nervous system activity increases when the inhibitory action of adenosine is blocked. Several other mechanisms of action, such as phosphodiesterase inhibition, have previously been proposed to explain the behavioral effects of caffeine. However, caffeine appears to exert its effects on adenosine receptors at much lower concentrations than that needed to affect any other *in vivo* mechanism.

#### 5. FACTORS AFFECTING INDIVIDUAL SENSITIVITY TO CAFFEINE

A variety of factors will modify the responsiveness of an individual to caffeine. In general the plasma half life of caffeine is 5-6 hours, with peak levels achieved from 15 to 45 minutes after ingestion (15,16). However, among cigarette smokers caffeine's half-life is only 3-4 hours (16). Oral contraceptive use appears to increase caffeine half life to approximately 11 hours and, in pregnant women, caffeine's half-life increases to 18 hours. In addition, there are data to suggest that are genetic differences in sensitivity to caffeine, although this has not been firmly established (17). Another critical factor determining an individual's sensitivity to caffeine is baseline level of caffeine consumption because tolerance develops when the substance is consumed on a regular basis (18). These individual differences, as well as the uncontrolled use of caffeine immediately prior to testing, must be considered when studies of caffeine are conducted. Furthermore, when recommendations concerning caffeine use are made to aircrew and ground personnel such individual factors must be carefully weighed.

#### 6. EFFECTS OF CAFFEINE ON BEHAVIOR

Although there have been more studies on the behavioral effects of caffeine than on any other food constituent, there exists only a very limited description of caffeine's effects on behavior. Comprehensive studies of caffeine's effects on human behavior have not been conducted, even though this substance is consumed on a daily basis in behaviorally active doses by hundreds of millions of people. Although we lack a comprehensive view of caffeine's effects on behavior, there is good evidence that its consumption, in

the doses found in single servings of foods, significantly affects certain key aspects of performance and mood state. Until recently even this simple conclusion was not generally agreed upon by a consensus of scientists (2).

#### 6.1 Vigilance

Although several papers appeared in the 70's indicating that caffeine in moderate doses would increase vigilance (19,20), later investigators were not always able to replicate these findings (21). The reasons for this inconsistency have been discussed in detail elsewhere and seem to be attributable to both the nature of the tasks employed to assess vigilance and differences in experimental design (1,2).

In an effort to reliably document the effects of caffeine on the behavior of normal individuals, including military personnel, my colleagues and I have developed several standardized testing paradigms that have consistently detected effects of caffeine on vigilance. In an initial study, we compared several vigilance tests and found that one in particular, the Wilkinson vigilance test (22), was sensitive to a wide range of caffeine doses (23). The Wilkinson test assesses sustained auditory vigilance and was initially developed to detect the effects of sleep deprivation on performance (22). The test is typically conducted for one hour without interruption. During the test period a 400 millisecond tone is presented once every two seconds. However, forty of the tones are approximately 70 milliseconds shorter than the rest and the subject must correctly identify these infrequent signal tones by responding on a computer keyboard. Task difficulty is equated from subject to subject by slightly varying the duration of the test stimuli. The original version of the test does not vary test duration across subjects (23).

Twenty males participated in our initial double-blind, crossover study. Caffeine consumption was restricted for 12 hours before each test day and smokers and individuals who normally consumed more than 400 mg of caffeine per day were excluded. Caffeine was administered in capsule form at 0800 h in doses of 32, 64, 128 and 256 mg and subjects were tested until 1100 h. Vigilance, as assessed by total number of correct detections on the Wilkinson task, was significantly improved by all four doses of caffeine. Error rate was not altered by caffeine administration (Fig. 2) (23). Effects were observed when only 32 mg of caffeine were administered, a dose not typically considered to be behaviorally active. In subsequent studies we have consistently documented effects of caffeine with the modified Wilkinson task. In one study we found that caffeine alone (64 mg) and caffeine (64 and 128 mg) in combination with aspirin, improved vigilance (24). In another study we replicated our original findings using 64 and 128 mg of caffeine (25). We have also observed similar effects of caffeine on women and elderly volunteers (Lieberman et al, unpublished observations), again using doses of 64, 128 and 256 mg.

# Effect of Caffeine on Auditory Vigilance

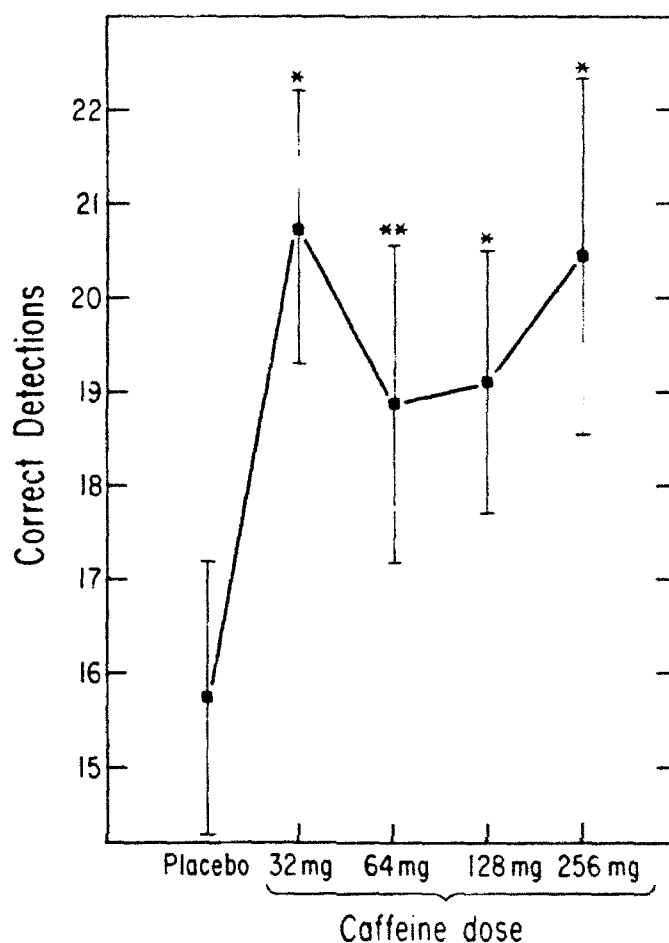


Figure 2. The effects of caffeine in doses of 32-256 mg and placebo on mean ( $\pm$ SEM) number of correct detections on the Wilkinson auditory vigilance task (\* indicates  $p < .005$  compared to placebo; \*\* indicates  $p < .01$  compared to placebo on post hoc tests)(23).

In a study recently conducted with 24 soldiers, we demonstrated that the effects of caffeine on vigilance could be also be readily detected with a specially designed test of visual vigilance (26). The test developed was of extended duration (two hours) and, like the Wilkinson vigilance task, had a low rate of critical signal presentation. During the test a rectangular cursor was presented for two seconds on the 9" x 11" monochrome video screen of an IBM-compatible personal computer. During the two hour test period there were 120 stimulus presentations. The cursor appeared at various locations on the screen so the subject had to continuously scan for its appearance. When a stimulus was detected, subjects were instructed to respond by pressing the space bar of their computer's keyboard.

As in the modified version of the Wilkinson vigilance task, difficulty was individually adjusted for each subject by varying the brightness of the cursor.

The study was conducted using 200 mg of caffeine administered at 0800 h. A double-blind, crossover design was employed. Caffeine significantly facilitated performance as assessed by number of correct detections and response time. The effects of caffeine were observed throughout the two hour test session as illustrated by Fig. 3. Unlike several previous studies (23-25) smokers and individuals who consume high levels of caffeine were not excluded from participation in this study and they responded differently to caffeine than other subjects (26).

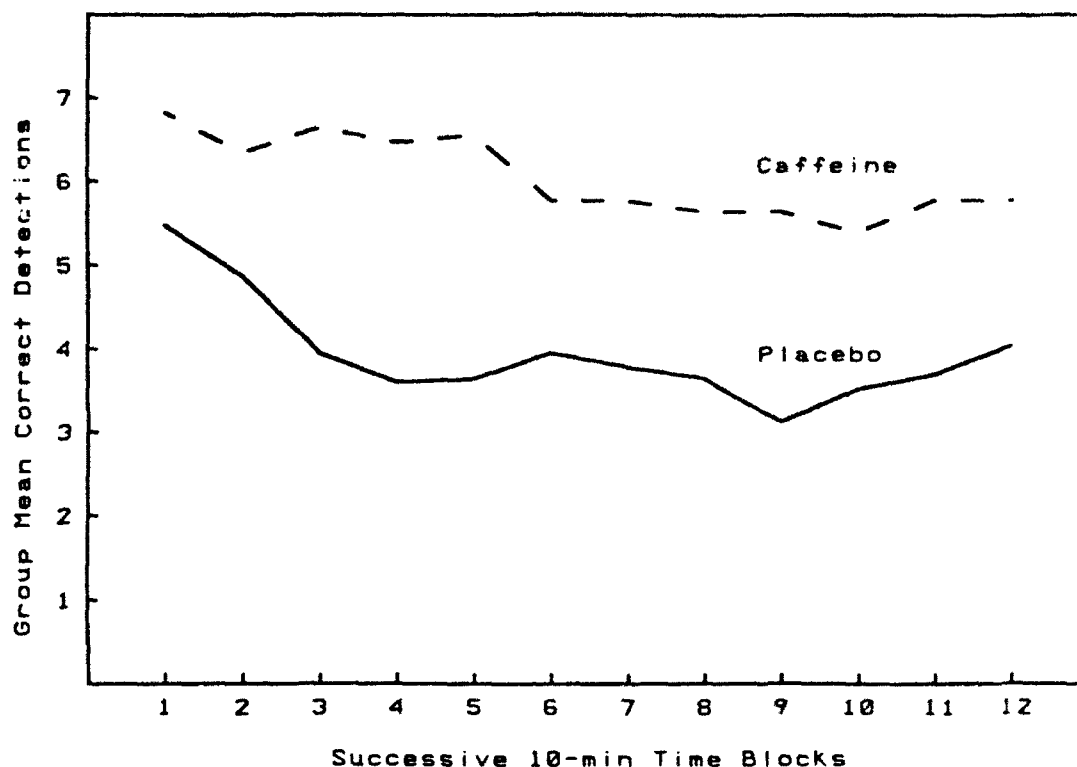


Figure 3. Mean number of correct detections in 10 minute time blocks for caffeine (200 mg) and placebo. The test employed assessed visual vigilance (26).

These studies demonstrate that caffeine can reliably increase vigilance when an appropriate task of the appropriate duration is employed in a well-controlled testing environment.

### 6.2 Psychomotor Performance and Cognition

Although vigilance appears to be the behavioral parameter most readily altered by caffeine consumption, there is evidence that certain other types of performance are also affected by caffeine consumption. Several studies have observed effects of caffeine on reaction time. When it is administered in low to moderate doses caffeine appears to facilitate responsiveness to stimuli (20,23,27,28), although not all investigators have reported such effects (29). In addition, at least one study found that high doses of caffeine, when administered to individuals who normally consume little caffeine, slowed responding (30). Another study reported that high doses of caffeine (600 mg) were not as effective as moderate doses (200 and 400 mg) at improving choice reaction time (28). In general, it seems likely that moderate doses of caffeine have positive, but difficult to detect, effects on simple and complex reaction time. Generalizations regarding the effects of caffeine on other aspects of performance are even more difficult to

reach. Complex cognitive functions, such as learning and memory do not appear to be sensitive to caffeine administration and little information is available on the effects of caffeine on sensory processing. For a recent review see Lieberman (2).

### 6.3 Simulator Studies

In spite of the widespread use of caffeine in the general population few studies have been conducted to determine whether caffeine may have beneficial or harmful effects in simulated or real work environments. In one study the effects of 200 mg of caffeine was tested on 24 young males in a laboratory simulation of long duration highway driving (19). In that study 200 mg of caffeine significantly improved several kinds of performance including response time to accelerations and decelerations of a lead car. The results of this study are similar to those investigating caffeine's effects on vigilance using laboratory tasks that reliably detect effects of caffeine.

In a study simulating a basic military task, sentry duty, Johnson (31) evaluated the effects of 200 mg of caffeine. Using a specially modified Weaponeer Rifle Marksmanship Simulator, which employs a modified M16A1 rifle,

performance was assessed for three hours after administration of caffeine or placebo. The soldiers participating in the study were required to respond to the infrequent appearance of a target by picking up a rifle and aiming and firing as rapidly, and accurately, as possible. Caffeine decreased detection time but did not significantly increase the total number of targets that were hit.

These studies would appear to have important practical implications for certain aviation related occupations. It is likely that when vigilance must be maintained for long periods of time, caffeine use may, in certain circumstances, be a critical factor. Furthermore, these postulated beneficial effects may increase in situations where vigilance is reduced due to jet lag, sleep loss, or circadian variations in arousal (2). Future studies, to extend these findings, should be conducted in a variety of aviation-related simulators, and when practical, in actual work environments. In addition, when certain accident investigations are conducted, it may be appropriate to determine if there have been changes in the normal patterns of caffeine use by the personnel involved.

#### 6.4 Effects of Caffeine on Mood State

While the effects of caffeine on many types of cognitive performance remain unresolved, there is little doubt that moderate doses of caffeine can significantly affect a variety of mood states. As would be expected from the effect that caffeine has on vigilance, its effects on mood appear greatest on those factors associated with alertness. For example, a number of studies have reported significant effects of caffeine, in doses of 64-200 mg, on the Vigor and Fatigue sub-scales of the Profile of Mood States (POMS) (24-26). The POMS is a self-report mood questionnaire often employed in psychopharmacologic studies (32). Other investigators have observed significant positive effects of caffeine on alertness, well-being, concentration, and a number of related states, when administered in a dose of 100 mg (28). In another study, increased alertness, vigor and decreased fatigue were observed when caffeine was administered in doses of 200, 400 and 600 mg (33). Some of the effects of caffeine on mood may be biphasic, depending on dose. Many individuals believe that caffeine increases anxiety, and at high doses, above 300 mg, this may be true, especially among individuals who do not normally consume large amounts of caffeine (34,35). However, at lower doses of 64-128 mg, which are more typical of those found in single servings of foods, caffeine may decrease anxiety, at least under certain circumstances (2,25).

#### 6.5 Adverse Behavioral Effects of Caffeine

It has been reported that consumption of more than 600 mg of caffeine per day may induce in normal individuals a syndrome known as "caffeinism", which is characterized by abnormally high levels of anxiety, poor sleep and somatic complaints similar to those seen among patients suffering from anxiety neuroses (36). In addition, caffeine has been linked, at least anecdotally, with impaired fine motor

performance. The scientific literature is contradictory on this issue. In a study discussed above, we found no evidence that doses of 32-256 mg of caffeine altered performance on complex motor tasks when low and moderate users were tested (23). However, Kuznicki and Turner (29) found that 160 mg, but not lower doses of caffeine, disrupted hand steadiness of individuals who did not usually consume caffeine, but had no adverse effects on regular caffeine consumers. As with other consequences of caffeine consumption, any adverse effects of caffeine on fine motor performance are dose-dependent and a function of the extent of habitual caffeine use by the individual.

Under certain circumstances caffeine appears to interfere with sleep, as would be expected from a compound that increases alertness. Adverse effects on sleep appear to be greatest when high doses of caffeine are consumed before bed by individuals who normally are not regular users of caffeine (2,37). However, many individuals report that they can consume coffee or other caffeine containing beverages before bedtime with no adverse effect (37,38).

The sudden withdrawal of caffeine from a diet that includes substantial amounts consumed on a regular basis, often appears to have adverse effects on the individual. Most notable is headache, which is relieved by consumption of caffeine. Caffeine-withdrawal headaches are also relieved by OTC analgesics and spontaneously remit after a few days of caffeine withdrawal (2,5). Such headaches may occur as the result of changes in vascular tone produced by hypersensitivity of adenosine receptors in the scalp and cranial blood vessels after caffeine withdrawal (39). Adverse effects of caffeine on mood-state, such as increased fatigue, have also been reported following its sudden withdrawal from the diet of heavy users (18).

The effects of caffeine withdrawal need to be carefully considered by flight surgeons and others since it may impair performance. Recommending the sudden withdrawal of caffeine from the diet could, at least theoretically, lead to serious adverse consequences with respect to job performance. It may be advisable for individuals who wish to reduce or eliminate caffeine from their diet to do so gradually (2). In addition, individuals who are heavy users of caffeine should be advised that its sudden withdrawal may produce a headache, adverse changes in mood-state and possibly impair performance.

It has been suggested that caffeine has addictive properties, and is similar in various respects to commonly abused substances (18). The evidence cited to support this association includes the adverse physical effects of caffeine withdrawal (for a review see Griffiths and Woodson, (40)), as well as certain animal and human behavioral research findings. This is a controversial area and although some scientists believe caffeine should be classified as a drug of abuse, others strongly disagree. For example, Hirsh (5)



states that caffeine has minimal abuse potential. In any case even scientists who believe caffeine can be abused concede that it has low abuse potential compared to more widely recognized drugs of abuse (40).

## 7. CONCLUSION

As discussed above, caffeine, when it is consumed in doses found in many foods, can improve the ability of individuals to perform tasks requiring sustained vigilance, including simulated automobile driving (2,19). Caffeine also improves the performance of soldiers engaged in a simulated marksmanship task that requires sustained vigilance for optimal performance (31). Sustained vigilance, particularly the ability to detect infrequent but critical stimuli, is essential for the optimal performance of many key aviation tasks, therefore it is likely that these beneficial effects will transfer to certain aviation related occupational duties.

Adverse behavioral effects of caffeine occur when it is consumed in excessive doses or by individuals who are overly sensitive to the substance (2). Higher than normal levels of anxiety may result and sleep may be affected. Since regular consumption of caffeine appears to produce tolerance to its behavioral effects, its sudden withdrawal from the diet may produce adverse symptoms such as headache and undesirable changes in mood state. The performance of individuals who are heavy consumers and have caffeine suddenly withdrawn from the diet may be impaired.

Unfortunately, the effects of caffeine on performance in actual or simulated flight operations or other aviation-related duties such as air traffic control have not been conducted. There is a critical need for such studies if rational recommendations are to be made to military planners, unit commanders, and flight surgeons regarding the use of caffeine by aircrew members.

Therefore, it is not possible to conclusively address the issues associated with the risks and benefits of caffeine use by aviation personnel. Positive behavioral consequences of caffeine consumption, such as increased ability to sustain vigilance and higher levels of self-reported alertness, are well documented. These beneficial effects clearly generalize to simulations of highway driving, sentry duty, and presumably similar aviation-related operations. It is possible that appropriate use of caffeine in such circumstances could prevent accidents attributable to lapses of vigilance (2). However, adverse effects of caffeine on sleep quality have been observed and some scientists believe that caffeine has many characteristics of an addictive drug. In addition, reports suggesting an association of caffeine consumption with the incidence of various diseases have appeared in the epidemiologic literature. However, at the current time no definitive data exist linking caffeine to any chronic disease and an expert panel has stated that "while questions about the ultimate safety of caffeine remain, there is solid evidence supporting

the view that moderate amounts are not harmful to the average healthy adult" (11).

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#### 9. ACKNOWLEDGEMENTS

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